

What is claimed is:

1. A method to propagate a recombinant viral vector comprising a nucleic acid sequence encoding an apoptosis-inducing protein, said method comprising culturing an isolated cell transfected with:
  - a. a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence; and,
  - b. a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence;
- 10 wherein said isolated cell is cultured under conditions effective to propagate said recombinant viral vector.
2. The method of Claim 1, further comprising recovering said recombinant viral vector from said isolated cell.
3. The method of Claim 1, wherein said recombinant nucleic acid molecule of (a) is contained within said recombinant viral vector of (b).
4. The method of Claim 3, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are operatively linked to different transcription control sequences.
5. The method of Claim 3, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are separated by an internal ribosome entry site (IRES).
6. The method of Claim 1, wherein said protein that inhibits apoptosis is selected from the group consisting of inhibitors of caspase-8 family activation and inhibitors of caspase-9 family activation.
7. The method of Claim 1, wherein said protein that inhibits apoptosis is a protein having biological activity of a protein selected from the group consisting of cowpox virus caspase inhibitor (CrmA), baculovirus p35, inhibitor of apoptosis protein (IAP),

dominant negative Fas-associating death domain-containing protein (dominant negative  
5 FADD), dominant negative Fas, FADD-like ICE inhibitory protein (FLIP), Bcl-2, Bcl-X<sub>L</sub>,  
and adenovirus E1B-19K protein.

8. The method of Claim 1, wherein said nucleic acid sequence encoding a  
protein that inhibits apoptosis encodes a protein comprising an amino acid sequence selected  
from the group consisting of SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID  
NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, and positions 80-208 of SEQ ID  
NO:14.

9. The method of Claim 1, wherein said nucleic acid sequence encoding a  
protein that inhibits apoptosis is selected from the group consisting of SEQ ID NO:37, SEQ  
ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID  
NO:49, and positions 367-753 of SEQ ID NO:13.

10. The method of Claim 1, wherein said protein that inhibits apoptosis is a  
protein having CrmA biological activity.

11. The method of Claim 1, wherein said protein that induces apoptosis has  
biological activity of a protein selected from the group consisting of Fas ligand, Fas, Fas-  
associating death domain-containing protein (FADD), Fas-associated death domain-like IL-  
1 $\beta$  converting enzyme (FLICE), tumor necrosis factor (TNF), TWEAK/Apo3L,  
5 TRAIL/Apo2L, Bax, Bid, Bik, Bad, Bak, and RICK.

12. The method of Claim 1, wherein said protein that induces apoptosis  
comprises an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ  
ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18,  
SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID  
5 NO:30, SEQ ID NO:32, SEQ ID NO:34 and SEQ ID NO:36.

13. The method of Claim 1, wherein said nucleic acid sequence encoding a  
protein that induces apoptosis is selected from the group consisting of SEQ ID NO:5, SEQ  
ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17,

SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID  
5 NO:29, SEQ ID NO:31, SEQ ID NO:33 and SEQ ID NO:35.

14. The method of Claim 1, wherein said recombinant viral vector is packaging deficient.

15. The method of Claim 1, wherein said recombinant viral vector is replication deficient.

16. The method of Claim 1, wherein said recombinant viral vector is from a virus selected from the group consisting of alphaviruses, poxviruses, adenoviruses, herpesviruses, lentiviruses, adeno-associated viruses, vaccinia viruses, baculoviruses, parvoviruses and retroviruses.

17. The method of Claim 1, wherein said recombinant viral vector is from an adenovirus.

18. The method of Claim 1, wherein said recombinant viral vector comprises a human adenovirus 5 construct under the control of a CMV immediate early promoter.

19. The method of Claim 18, wherein said human adenovirus 5 construct is replication deficient.

20. The method of Claim 1, wherein said recombinant viral vector comprises a nucleic acid sequence represented by at least a portion of SEQ ID NO:4.

21. The method of Claim 1, wherein said isolated cell is a mammalian cell.

22. The method of Claim 1, wherein said isolated cell produces at least about  $1 \times 10^8$  plaque forming units (pfu) of said recombinant viral vector per ml of supernatant isolated from said cell.

23. The method of Claim 1, wherein said isolated cell produces at least about  $5 \times 10^8$  pfu of said recombinant viral vector per ml of supernatant isolated from said cell.

24. The method of Claim 1, wherein said isolated cell produces at least about  $1 \times 10^9$  pfu of said recombinant viral vector per ml of supernatant isolated from said cell.

25. An isolated cell, wherein said cell is transfected with:

a. a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence; and,

5 b. a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence.

26. The cell of Claim 25, wherein said recombinant nucleic acid molecule of (a) is contained within said recombinant viral vector of (b).

27. The cell of Claim 26, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are operatively linked to different transcription control sequences.

28. The cell of Claim 26, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are separated by an internal ribosome entry site (IRES).

29. The cell of Claim 25, wherein said protein that inhibits apoptosis is selected from the group consisting of inhibitors of caspase-8 family activation and inhibitors of caspase-9 family activation.

30. The cell of Claim 25, wherein said protein that inhibits apoptosis is a protein having biological activity of a protein selected from the group consisting of cowpox virus caspase inhibitor (CrmA), baculovirus p35, inhibitor of apoptosis protein (IAP), dominant negative Fas-associating death domain-containing protein (dominant negative FADD),  
5 dominant negative Fas, FADD-like ICE inhibitory protein (FLIP), Bcl-2, Bcl-X<sub>L</sub>, and adenovirus E1B-19K protein..

31. The cell of Claim 25, wherein said protein that induces apoptosis has biological activity of a protein selected from the group consisting of Fas ligand, Fas, Fas-associating death domain-containing protein (FADD), Fas-associated death domain-like IL-

1 $\beta$  converting enzyme (FLICE), tumor necrosis factor (TNF), TWEAK/Apo3L,  
5 TRAIL/Apo2L, Bax, Bid, Bik, Bad, Bak, and RICK.

32. The cell of Claim 25, wherein said recombinant viral vector is from a virus selected from the group consisting of alphaviruses, poxviruses, adenoviruses, herpesviruses, lentiviruses, adeno-associated viruses, vaccinia viruses, baculoviruses, parvoviruses and retroviruses.

33. The cell of Claim 25, wherein said isolated cell produces at least about  $1 \times 10^8$  pfu of said recombinant viral vector per ml of supernatant isolated from said cell.

34. The cell of Claim 25, wherein said cell is a mammalian cell.

35. A recombinant viral vector for inducing apoptosis in cells transfected with said vector, said viral vector comprising a recombinant virus comprising:

- a. an isolated nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence; and,
- b. an isolated nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence.

36. The viral vector of Claim 35, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are operatively linked to different transcription control sequences.

37. The viral vector of Claim 35, wherein said nucleic acid sequence of (a) and said nucleic acid sequence of (b) are separated by an internal ribosome entry site (IRES).

38. The viral vector of Claim 35, wherein said protein that inhibits apoptosis is selected from the group consisting of inhibitors of caspase-8 family activation and inhibitors of caspase-9 family activation.

39. The viral vector of Claim 35, wherein said protein that inhibits apoptosis is a protein having biological activity of a protein selected from the group consisting of cowpox virus caspase inhibitor (CrmA), baculovirus p35, inhibitor of apoptosis protein (IAP), dominant negative Fas-associating death domain-containing protein (dominant negative FADD), dominant negative Fas, FADD-like ICE inhibitory protein (FLIP), Bcl-2, Bcl-X<sub>L</sub>, and adenovirus E1B-19K protein.

40. The viral vector of Claim 35, wherein said protein that induces apoptosis has biological activity of a protein selected from the group consisting of Fas ligand, Fas, Fas-associating death domain-containing protein (FADD), Fas-associated death domain-like IL-1 $\beta$  converting enzyme (FLICE), tumor necrosis factor (TNF), TWEAK/Apo3L, TRAIL/Apo2L, Bax, Bid, Bik, Bad, Bak, and RICK.

41. The viral vector of Claim 35, wherein said recombinant viral vector is from a virus selected from the group consisting of alphaviruses, poxviruses, adenoviruses,

herpesviruses, lentiviruses, adeno-associated viruses, vaccinia viruses, baculoviruses, parvoviruses and retroviruses.

42. The viral vector of Claim 35, wherein said recombinant viral vector comprises a nucleic acid sequence represented by at least a portion of SEQ ID NO:4.

43. A recombinant viral vector comprising:

a. an isolated human adenovirus 5 construct encoded by a nucleic acid sequence comprising at least a portion of SEQ ID NO:4; and,

b. a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding Fas ligand or a biologically active fragment thereof, operatively linked to a transcription control sequence.

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44. A method of suppressing T-lymphocyte-mediated graft rejection in a recipient mammal, said method comprising introducing into said mammal a pharmaceutically acceptable carrier comprising a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence, wherein said recombinant viral vector expresses said protein that induces apoptosis.

45. The method of Claim 44, wherein said pharmaceutically acceptable carrier further comprises a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence.

46. The method of Claim 45, wherein said recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis is contained within said recombinant viral vector.

47. The method of Claim 46, wherein said nucleic acid sequence encoding a protein that inhibits apoptosis and said nucleic acid sequence encoding a protein that induces apoptosis are operatively linked to different transcription control sequences.

48. The method of Claim 46, wherein said nucleic acid sequence encoding a protein that inhibits apoptosis and said nucleic acid sequence encoding a protein that induces apoptosis are separated by an internal ribosome entry site (IRES).

49. The method of Claim 45, wherein said pharmaceutically acceptable carrier is an isolated cell that is transfected with said recombinant nucleic acid molecule and said recombinant viral vector.

50. The method of Claim 44, wherein said pharmaceutically acceptable carrier is selected from the group consisting of an isolated cell and a pharmaceutically acceptable excipient.

51. The method of claim 50, wherein said cell is a cell of said graft.

52. The method of claim 50, wherein said cell is not a part of said graft.

53. The method of Claim 50, wherein said cell is an islet cell.

54. A method of inducing apoptosis in cancer cells of a recipient mammal, comprising introducing into said mammal a recombinant viral vector comprising:

a. a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence; and,

b. a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence;

wherein said protein that induces apoptosis is expressed by a cell at or adjacent to a site of said cancer, and wherein said expression of said protein at said site of said cancer is sufficient to produce a result selected from the group consisting of: reduction of tumor size, elimination of tumor cells at said site; prevention of tumor growth at said site and prevention of metastases from said tumor cells.

55. The method of Claim 54, wherein said cancer is selected from the group consisting of lung cancer, brain cancer, prostate cancer, lymphoma and leukemia.

56. A method of suppressing a T-lymphocyte-mediated disease in a recipient mammal, said method comprising introducing into said mammal a pharmaceutically acceptable carrier comprising a recombinant viral vector comprising a nucleic acid sequence encoding a protein that induces apoptosis operatively linked to a transcription control sequence, wherein said recombinant viral vector expresses said protein that induces apoptosis.

57. The method of Claim 56, wherein said pharmaceutically acceptable carrier further comprises a recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis operatively linked to a transcription control sequence.

58. The method of Claim 57, wherein said recombinant nucleic acid molecule comprising a nucleic acid sequence encoding a protein that inhibits apoptosis is contained within said recombinant viral vector.

59. The method of Claim 58, wherein said nucleic acid sequence encoding a protein that inhibits apoptosis and said nucleic acid sequence encoding a protein that induces apoptosis are operatively linked to different transcription control sequences.

60. The method of Claim 58, wherein said nucleic acid sequence encoding a protein that inhibits apoptosis and said nucleic acid sequence encoding a protein that induces apoptosis are separated by an internal ribosome entry site (IRES).

61. The method of Claim 57, wherein said pharmaceutically acceptable carrier is an isolated cell that is transfected with said recombinant nucleic acid molecule and said recombinant viral vector.

62. The method of Claim 56, wherein said pharmaceutically acceptable carrier is selected from the group consisting of an isolated cell and a pharmaceutically acceptable excipient.

63. The method of Claim 56, wherein said T lymphocyte-mediated disease is selected from the group consisting of rheumatoid arthritis, insulin-dependent diabetes

mellitus, multiple sclerosis, lupus erythematosus, myasthenia gravis, and graft versus host reactions.